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| EXAMINER | |
|---|---|
| POHNERT, STEVEN C | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/801,956 | FUJIMOTO ET AL. | |
| | Examiner | Art Unit | |
| | Steven C. Pohnert | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-3,6-8,12,13,26-28,35-37,44-47,52,53,58-61,74,81,82 and 85-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-8,12,13,26-28,35-37,44-47,52,53,58-61,74,81,82 and 85-92* is/are rejected.

7)☒ Claim(s) *35-37,58-61,87,88,91 and 92* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application

6)☐ Other: _____.

**DETAILED ACTION**

This action is in response to the claim amendment filed 8/21/2008 and the arguments filed 6/6/2008.

The claims 4-5, 9-11, 14-25, 29-34, 38-43, 48-51, 54-57, 62-73, 75-80, 83-84 and 93-96 are canceled.

Claims 1-3, 6-8, 12-13, 26-28, 35-37, 44-47, 52-53, 58-61, 74, 81-82, 85-92 are pending.

The objection to claims 6-8, 12-13, 26-28, 35-37, 44-47, 49, 52-53, 58-61, 74, 81-82, and 85-92 have been withdrawn due to the amendment.

The New matter rejection to claims 26-28, 30, 44-47, 49, 52, 53, 85, 86 89 and 90 has been withdrawn in view of the amendment.

The enablement and written description rejections have been withdrawn in view of the amendment. The amendment of these claims that necessitated the withdraw of the enablement and written description rejections now present art rejections.

The 112-2$^{nd}$ paragraph rejections of claims 17-19, 21, 83 and 84 has been withdrawn in view of the cancellation of the claims.

The 102 rejection of claims 1, 5, 6, 10, 12, 13, 17 based on Soengas has been withdrawn in view claim amendments.

The double patenting rejection has been withdrawn in view of the amendment to require specific markers that are not taught by co-pending 10/809,956.

***Claim Objections***

1. Claims 35-37, 58-61, 87-88 and 91-92 are objected to because of the following informalities:

Claims 35 and 58 recite, "Interferon, and alpha-2b." This appears to be typographical error as the specification teaches, "interferon $\alpha$-2b" on page 31, line 15. This objection can easily be overcome by amending the claims to recite, "Interferon alpha-2b." As all dependent claims have all the limitations of the independent claims they are objected to for the same reasons.

Claim 58 is further objected to as it recites, "to a round melanoma biochemotherapy." This appears to be a typographical error and can easily be overcome by amending the claim to recite, "To a round of melanoma biochemotherapy." As all dependent claims have all the limitations of the independent claims they are objected to for the same reasons.

Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 27, 28, 36, 37, 46, 47, 60, 61, and 87-92 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims 27, 28, and 85 are dependent on claim 26 and require, "wherein the sample is a serum sample" (claim 27), or "wherein the sample is a plasma sample"

(claim 28), "wherein the sample is a blood sample" (claim 86), however, claim 26 requires providing a melanoma tissue sample. It is thus unclear the metes and bounds of claims 27 and 28 as it is unclear how a melanoma tissue sample can also be a serum sample or a plasma sample. This rejection can be overcome by canceling claims 27 and 28.

The claims 36 and 37 are dependent on claim 35 and require, " wherein the sample is a serum sample" or "wherein the sample is a plasma sample," however, claim 35 requires providing a melanoma tissue sample. It is thus unclear the metes and bounds of claims 36 and 37 as it is unclear how a melanoma tissue sample can also be a serum sample or a plasma sample. This rejection can be overcome by canceling claims 36 and 37.

The claims 46 and 47 are dependent on claim 44 and require, " wherein the sample is a serum sample" or "wherein the sample is a plasma sample," however, claim 44 requires providing a melanoma tissue sample. It is thus unclear the metes and bounds of claims 46 and 47 as it is unclear how a melanoma tissue sample can also be a serum sample or a plasma sample. This rejection can be overcome by canceling claims 46 and 47.

The claims 60 and 61 are dependent on claim 58 and require, " wherein the sample is a serum sample" or "wherein the sample is a plasma sample," however, claim 58 requires providing a melanoma tissue sample. It is thus unclear the metes and bounds of claims 60 and 61 as it is unclear how a melanoma tissue sample can also be

a serum sample or a plasma sample. This rejection can be overcome by canceling claims 60 and 61.

The claims 87 and 88 are dependent on claim 35 and require, "wherein the DNA exists as accellular DNA in the subject" (claim 87) or "wherein the sample is a blood sample" (claim 88) however, claim 35 requires providing a melanoma tissue sample containing DNA. It is thus unclear the metes and bounds of claims 87 and 88 as it is unclear how a melanoma tissue sample can also be a blood sample or a tissue sample can comprise DNA that is extracellular in the subject. This rejection can be overcome by canceling claims 87 and 88.

The claims 89 and 90 are dependent on claim 44and require, "wherein the DNA exists as accellular DNA in the subject" (claim 89) or "wherein the sample is a blood sample" (claim 90), however, claim 44 requires providing a melanoma tissue sample containing DNA. It is thus unclear the metes and bounds of claims 89 and 90 as it is unclear how a melanoma tissue sample can also be a blood sample or a tissue sample can comprise DNA that is extracellular in the subject. This rejection can be overcome by canceling claims 89 and 90.

The claims 91 and 92 are dependent on claim 58 and require, "wherein the DNA exists as accellular DNA in the subject" (claim 91) or "wherein the sample is a blood sample" (claim 92), however, claim 44 requires providing a melanoma tissue sample containing DNA. It is thus unclear the metes and bounds of claims 91 and 92 as it is unclear how a melanoma tissue sample can also be a blood sample or a tissue sample

can comprise DNA that is extracellular in the subject. This rejection can be overcome by canceling claims 91 and 92.

***Claim Rejections - 35 USC § 102***

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claim 26 rejected under 35 U.S.C. 102(b) as being anticipated by Soengas, et al (Nature, 2001, volume 409, pages 207-211).

This rejection is a new ground of rejection necessitated by amendment.

Soengas et al teaches detection of loss of heterozygosity of 12q22-23 region in 24 patients using 6 12q22-23 microsatellite markers including D12S1657, D12S393, D12S1706, and D12S346 (see figure 1 and legend). Soengas further teaches genomic DNA for tumor and normal cells were amplified by PCR.

Soengas teaches loss of APAF1 and microsatellite markers (D12S1657, D12S393, D12S1706, and D12S346) in the 12q22-23 regions in patients are detected in metastatic melanoma (see abstract; page 207 2nd column, lines12-14). Soengas further teaches genomic DNA for tumor and normal cells were amplified by PCR. Soengas teaches there is a high rate of APAF-1 LOH (including D12S1657, D12S393, D12S1706, and D12S346) in metastatic melanoma (see page 207, column 2, lines 17-19), but not in primary melanoma (see page 208, 1st column, line 1). Soengas thus

teaches LOH of APAF-1 (including D12S1657, D12S393, D12S1706, and D12S346) in melanoma indicates a high probability of metastatic cancer.

Soengas teaches loss of APAF-1 is associated with disease progression (see page 208, lines 2-4).

Soengas conclude by stating that, "our results imply the APAF-1 loss contributes to the aggressive nature and extreme chemoresistance of metastatic melanoma" page 210 2nd column, and last paragraph).

Soengas thus teaches a method of detecting melanoma by loss of heterozygosity for DNA markers D12S1657, D12S393, D12S1706, and D12S346, indicates progression of melanoma.

**Response to Arguments**

This is a new ground of rejection necessitated by amendment. There are no arguments of record as the art.

***Claim Rejections - 35 USC § 103***

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-3, 6, 7, 8, 12, 13, 74, 81, and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soengas, et al (Nature, 2001, volume 409, pages 207-211) in view of Gocke et al (US Patent 6156504, issued Dec 5, 2000).

As noted in the MPEP 211.02, "a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." Further, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, "then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation." In the present situation, steps of independent claims 1 and 6 are able to stand-alone and the preamble limitation is not accorded patentable weight. Accordingly, the claim language of the preamble to claim 1 merely sets forth the intended use or purpose of the claimed methods, but does not limit the scope of the claims.

This rejection was previously presented but has been modified to reflect the claim amendments and improve clarity.

Soengas et al teaches detection of loss of heterozygosity of 12q22-23 region in 24 patients using 6 12q22-23 microsatellite markers including D12S1657, D12S393, D12S1706, and D12S346 (see figure 1 and legend). Soengas further teaches genomic DNA for tumor and normal cells were amplified by PCR.

Soengas teaches loss of APAF1 and microsatellite markers (D12S1657, D12S393, D12S1706, and D12S346) in the 12q22-23 regions in patients are detected in metastatic melanoma (see abstract; page 207 2nd column, lines12-14). Soengas further teaches genomic DNA for tumor and normal cells were amplified by PCR. Soengas teaches detecting cancer by LOH of markers D12S1657, D12S393, D12S1706, and D12S346.

Soengas teaches there is a high rate of APAF-1 LOH in metastatic melanoma (see page 207, column 2, lines 17-19), but not in primary melanoma (see page 208, 1st column, line 1). Soengas thus teaches LOH of APAF-1 in melanoma indicates a high probability of metastatic cancer.

Soengas teaches loss of APAF-1 is associated with disease progression (see page 208, lines 2-4).

Soengas teaches there is correlation of APAF-1 levels and response to Adriamycin in melanoma cells (see page 209, column 1, lines 8-10). Soengas teaches that APAF-1 levels are lower in melanomas with APAF-1 LOH. Soengas thus teaches APAF-1 LOH results in poor efficacy of treatment in melanoma.

Soengas does not teach the use of accellular DNA from plasma (claims 3, 8), serum (2, 7), or blood (claims 81, 82,) as a sample.

However, Gocke et al teaches methods of using of extracellular DNA found serum (2, 7) or plasma (claims 3,8,) for the detection of cancer (see title, abstract). Gocke teaches peripheral blood (claims 81, 82,); plasma or serum is easily accessible and amenable for DNA amplification (see column 2, lines 54-55). Gocke et al further teaches that many studies have used nucleic acid amplification to detect intracellular DNA extracted from circulating cells in blood (see column 2, line 56-60). Gocke teaches use of blood, plasma, or serum allows rapid and timely extraction and sensitive detection of extra cellular tumor associated or extracellular mutated oncogenic DNA (see column 3, lines 60-63).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Soengas method of detecting markers D12S1657, D12S393, D12S1706, and D12S346 by use of peripheral blood, plasma, or serum as taught by Gocke, because Gocke teaches blood, plasma, or serum is easily accessible and amenable for DNA amplification and thus detection of nucleic acids. The ordinary artisan would further be motivated because, Gocke teaches use of plasma or serum allows rapid and timely extraction and sensitive detection of extracellular tumor associated or extracellular mutated oncogenic DNA. Thus as Gocke teaches methods of nucleic acid analysis by PCR amplification as taught by Soengas the artisan would have a reasonable expectation of success. The combination of Soengas and Gocke would have resulted in a method of detecting the presence or absence of D12S1657, D12S393, D12S1706, and D12S346 markers in accellular DNA from blood, serum, or plasma and from this detection allow the detection of melanoma.

**Response to Arguments**

The response of 6/06/2008 asserts that Soengas does not teach detecting molecular markers of accellular DNA from serum or plasma (claim 1) or detecting melanoma from accellular DNA for detection of melanoma (claim 6). The response further asserts that the teachings of Goecke do not overcome these deficiencies. The response asserts that Gocke is cited for the use of serum or plasma for DNA amplification. It is noted that a prior art reference is considered as a whole and for all it stands for. These arguments have been thoroughly reviewed but are not considered persuasive Goecke teaches a method of detecting cancer by use of extracellular DNA and Soengas teaches loss of D12S1657, D12S393, D12S1706, and D12S346 is common in melanoma. Thus the teachings of Soengas and Gocke teach and /or suggest every limitation of the claims thus rendering the instant claims obvious. The combination of Soengas and Gocke is a combination of two known methods for the detection of nucleic acids for the purpose of detecting cancer.

9. Claims 35, 58-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soengas, et al (Nature, 2001, volume 409, pages 207-211) in view of O'Day et al (Journal of Clinical Oncology (1999) volume 17, pages 2752-2761).

In claims 35 and 58 the recitation of "interferon, alpha-2b" is being interpreted as "interferon alpha-2b" which is taught in the specification on page 31, line 15.

With regards to claims 35, Soengas teaches there is correlation of APAF-1 levels and response to adriamycin in melanoma cells (see page 209, column 1, lines 8-10). Soengas teaches that APAF-1 levels are lower in melanoma's due to APAF-1 LOH.

Soengas teaches detection of LOH for APAF-1 by assaying markers D12S1657, D12S393, D12S1706, and D12S346 (see figure 1B). Soengas thus teaches D12S1657, D12S393, D12S1706, and D12S346 LOH results in poor efficacy of treatment in melanoma.

With regards to claim 58, Soengas teaches assessment of teaches D12S1657, D12S393, D12S1706, and D12S346 status improves therapeutic management for patients, as it is a required for apoptosis and thus a marker of chemosensitivity (see page 210, 2nd column, lines 20-26).

With regards to claim 59, Soengas teaches LOH analysis from tumor samples (see page 210, 2nd column, analysis of APAF-1 locus).

Soengas does not teach that loss of heterozygosity of D12S1657, D12S393, D12S1706, and D12S346 is predictive of response to biochemotherapy or predicted efficacy of response to biochemotherapy. Soengas does not teach melanoma biochemotherapy comprising dacarbazine, cisplatin, vinblastin, interferon alpha-2b, IL-2 and tamoxifen.

However, Soengas teaches "Assessment of Apaf-1status may therefore improve the therapeutic management of patients with malignant melanoma" (see page 210, 2nd column last line of text).

Further O'Day et al teaches "5-day modified concurrent biochemotherapy regimen of dacarbazine, vinblastine, cisplatin, decrescendo IL-2, interferon alpha-2b, and tamoxifen was repeated at 21-day intervals" (see abstract). O'Day teaches pretreatment evaluation (page 2753, 2nd column). O'Day further teaches, "the

concurrent biochemotherapy regime of Legha et al was modified in an effort to reduce toxicity further while maintaining or improving efficacy. These modifications consisted of decrescendo IL-2 dosing, routine use of growth factor support with granulocyte colony-stimulating factor (G-CSF), and low-dose tamoxifen. The total IL-2 dose was unchanged, but this agent was administered in a decrescendo schedule, with a higher initial dose in the first 24 hours that decreased progressively on subsequent days. This change in IL-2 dosing is based on preclinical and clinical studies suggesting that decrescendo dosing improves efficacy and reduces cumulative IL-2 toxicity.29, 30 Routine post treatment G-CSF was implemented because of the high incidence of grade
myelosuppression, fever/neutropenia, and infection in Legha's concurrent biochemotherapy trial. Tamoxifen was added to the regimen because at the time the study was designed, data suggested potential synergistic effects with chemotherapy" (page 27531$^{st}$ column, 2$^{nd}$ full paragraph).

Therefore, it would be prima facie obvious to one of skill in the art at the time the invention was made to predict efficacy of response to dacarbazine, vinblastine, cisplatin, decrescendo IL-2, interferon alfa-2b, and tamoxifen in patients or the probability of responsiveness to dacarbazine, vinblastine, cisplatin, decrescendo IL-2, interferon alfa-2b, and tamoxifen in view of the teachings of Soengas with a reasonable expectation of success. The teachings of Soengas suggest that loss of heterozygosity of D12S1657, D12S393, D12S1706, and D12S346 markers results decreased apoptosis, which in turn results in increased chemoresistance to chemotherapeutic agents. Thus, it would have

been obvious to one of skill in the art LOH of markers known to be associated with decreased apoptosis in response to treatment with one apoptosis inducing chemotherapeutic drug (adriamycin) would also be associated with decreased apoptosis and thus chemoresistance to other known chemotherapeutic agents (dacarbazine, vinblastine, cisplatin, decrescendo IL-2, interferon alfa-2b, and tamoxifen), absent secondary consideration. It would have been obvious to one of skill in the art in view of the teachings of Soengas and O'Day to use D12S1657, D12S393, D12S1706, and D12S346 to predict responsiveness or efficacy of treatment as Soengas teaches "Assessment of Apaf-1status may therefore improve the therapeutic management of patients with malignant melanoma" (see page 210, 2nd column last line of text). The artisan would be motivated because Soengas suggest such a method as cited above. The artisan would have a reasonable expectation of success as the artisan would merely be using an assay to predict the response to a known biochemotherapy.

**Response to arguments**

The response asserts that the instant claims are not obvious over the teachings of Soengas as Soengas does not teach biochemotherapy comprising dacarbazine, vinblastine, cisplatin, decrescendo IL-2, interferon alfa-2b, and tamoxifen. The examiner concurs and thus has presented the instant rejection. The response further asserts that Soengas does not teach or disclose using type IV melanoma. This argument is moot as there are no claims that depend from claim 35 or 58 that require type IV melanoma.

10. Claims 44 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soengas, et al (Nature, 2001, volume 409, pages 207-211) in view of Taback et al (Cancer Research (2001) volume 61, pages 5723-5726).

This rejection is a new ground of rejection necessitated by amendment.

Soengas et al teaches detection of loss of heterozygosity of 12q22-23 region in 24 patients using 6 12q22-23 microsatellite markers including D12S1657, D12S393, D12S1706, and D12S346 (see figure 1 and legend). Soengas further teaches genomic DNA for tumor and normal cells were amplified by PCR.

Soengas teaches loss of APAF1 and microsatellite markers (D12S1657, D12S393, D12S1706, and D12S346) in the 12q22-23 regions in patients are detected in metastatic melanoma (see abstract; page 207 2nd column, lines12-14). Soengas further teaches genomic DNA for tumor and normal cells were amplified by PCR. Soengas teaches there is a high rate of APAF-1 LOH (including D12S1657, D12S393, D12S1706, and D12S346) in metastatic melanoma (see page 207, column 2, lines 17-19), but not in primary melanoma (see page 208, 1st column, line 1). Soengas thus teaches LOH of APAF-1 (including D12S1657, D12S393, D12S1706, and D12S346) in melanoma indicates a high probability of metastatic cancer.

Soengas teaches loss of APAF-1 is associated with disease progression (see page 208, lines 2-4).

Soengas conclude by stating that, "our results imply the APAF-1 loss contributes to the aggressive nature and extreme chemoresistance of metastatic melanoma" page 210 2nd column, and last paragraph).

Soengas thus teaches a method of detecting melanoma by loss of heterozygosity for DNA markers D12S1657, D12S393, D12S1706, and D12S346, indicates progression of melanoma.

Soengas does not teach providing samples with stage III or Stage IV melanoma.

However, Taback teaches loss of heterozygosity of microsatelite markers in stage III and stage IV melanoma is associated with a decreased probability of survival (figure 1). Taback teaches, "The findings of additional LOH in more advanced tumors (i.e., highly invasive primary lesions and advanced metastasis) suggests that these additional events, not always present in early stages of primary tumors, may be associated with, or representative of, more aggressive tumors that may be of prognostic value" (page 5723, 2nd column, 1st paragraph). Taback further teaches that once melanoma has metastasized, overall prognosis is generally poor (page 5725, 1st column, 1st full paragraph).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to analyze stage III or stage IV melanoma as taught by Taback in the method of Soengas. The artisan would be use stage III or stage IV melanoma samples in the method of Soengas as there are only four stages of melanoma known and thus a limited number of possibilities. The artisan would have a reasonable expectation of success of determining a low probability of survival of patients with LOH of stage III and stage IV melanoma have a poor prognostic outcome and further because Soengas teaches LOH of D12S1657, D12S393, D12S1706, and

D12S346 is associated with decreased apoptosis in response to chemotherapy and thus poor outcome.

11. Claims 52 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soengas, et al (Nature, 2001, volume 409, pages 207-211) and of Taback et al (Cancer Research (2001) volume 61, pages 5723-5726) as applied to claim 44 and 45 above, and further in view of Yu et al (Cancer (1999) volume 86, pages 612-627).

The teachings of Soengas and Taback are set forth above in paragraph 10.

Soengas and Taback do not teach melanoma being regional lymph node metastasis (RLM) or in transit metastasis (ITM).

However, Yu teaches early detection of AJCC stage III metastasis's to regional lymph nodes (RLM) (page 625, 2nd column 1st paragraph). Yu further teaches melanoma metastasis in transit were known (page 620, 1st column, 1st full paragraph).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to analyze IRM or ITM melanoma as taught by Yu in the method of Soengas and Taback. The artisan would be use IRM or ITM melanoma samples in the method of Soengas and Taback as there are known forms of melanoma mestasis. The artisan would have a reasonable expectation of success of determining a low probability of survival of patients with metastatic melanoma including IRM and ITM because Soengas teaches LOH of D12S1657, D12S393, D12S1706, and D12S346 is associated with decreased apoptosis in response to chemotherapy and thus poor outcome.

***Conclusion***

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is (571)272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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